

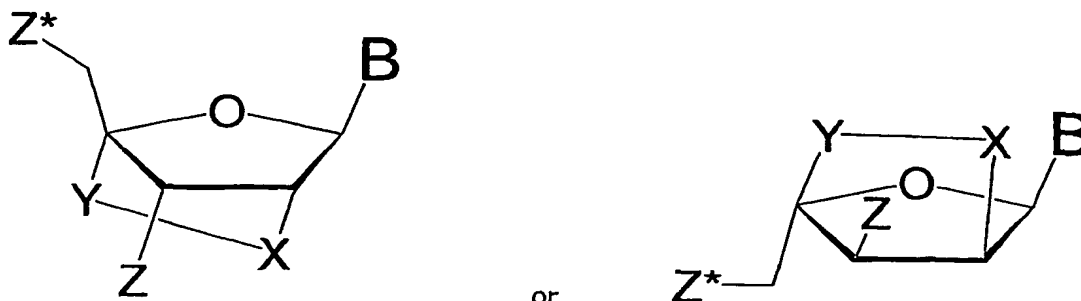
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(51)

CLAIMS

1. A double-stranded compound comprising a sense strand and an antisense strand,
wherein each strand comprises 12-35 nucleotides and wherein said compound comprises
5 at least one locked nucleic acid (LNA) monomer having the structure



wherein

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X is selected from the group consisting of O, S and NR^{H} , where R^{H} is H or C_{1-4} -alkyl;

Y is CH_2 ;

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B is a nucleobase;

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Z and Z^* are independently absent or selected from the group consisting of an internucleoside linkage group, a terminal group and a protection group; so that when the LNA monomer is located at the 3' end, Z is a terminal group and Z^* is an internucleoside linkage group; when the LNA monomer is located at the 5' end, Z is absent and Z^* is a terminal group; and when the LNA monomer is located within the nucleotide sequence, Z is absent and Z^* is an internucleoside linkage group.

2. The compound according to claim 1, wherein the sense strand comprises at least one
25 LNA monomer.

3. The compound according to claim 2, wherein the sense strand comprises 1-10 LNA monomers.

- 30 4. The compound according to claim 2 or 3, wherein at least one LNA monomer is located at the 5' end of the sense strand.

5. The compound according to claim 4, wherein at least two LNA monomers are located at the 5' end of the sense strand
6. The compound according to any of the preceding claims, wherein at least one LNA monomer is located at the 3' end of the sense strand.
7. The compound according to claim 6, wherein at least two LNA monomers are located at the 3' end of the sense strand.
- 10 8. The compound according to any of the preceding claims, wherein the antisense strand comprises at least one LNA monomer.
9. The compound according to claim 8, wherein the antisense strand comprises 1-10 LNA monomers.
- 15 10. The compound according to claim 8 or 9, wherein at least one LNA monomer is located at the 3' end of the antisense strand.
11. The compound according to claim 10, wherein at least two LNA monomers are located at the 3' end of the antisense strand.
- 20 12. The compound according to claim 11, wherein at least three LNA monomers are located at the 3' end of the antisense strand.
13. The compound according to any of the preceding claims, wherein no LNA monomer is located at the 5' end of the antisense strand.
14. The compound according to any of the preceding claims, wherein the sense strand comprises at least one LNA and the antisense strand comprises at least one LNA monomer.
- 30 15. The compound according to claim 14, wherein the sense strand comprises 1-10 LNA monomers and the antisense strand comprises 1-10 LNA monomers.
16. The compound according to claim 14 or 15, wherein the sense strand comprises at least one LNA monomer at the 5' end and at least one LNA monomer at the 3' end, and wherein the antisense strand comprises at least one LNA monomer at the 3' end.
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17. The compound according to claim 16, wherein the sense strand comprises at least one LNA monomer at the 5' end and at least one LNA monomer at the 3' end, and wherein the antisense strand comprises at least two LNA monomers at the 3' end.
- 5 18. The compound according to claim 17, wherein the sense strand comprises at least two LNA monomers at the 5' end and at least two LNA monomers at the 3' end, and wherein the antisense strand comprises at least two LNA monomers at the 3' end.
19. The compound according to claim 18, wherein the sense strand comprises at least two
10 LNA monomers at the 5' end and at least two LNA monomers at the 3' end, and wherein the antisense strand comprises at least three LNA monomers at the 3' end.
20. The compound according to any of claims 14-19, wherein no LNA monomer is located at the 5' end of the antisense strand.
- 15 21. The compound according to any of the preceding claims, wherein the sense strand comprises at least one LNA monomer in at least one of the positions 9-13 counted from the 5' end.
- 20 22. The compound according to claim 21, wherein the sense strand comprises a LNA monomer in position 10.
23. The compound according to claim 21 or 22, wherein the sense strand comprises a LNA monomer in position 11.
- 25 24. The compound according to any of claims 21-23, wherein the sense strand comprises a LNA monomer in position 12.
25. The compound according to any of the preceding claims, wherein each strand
30 comprises 17-25 nucleotides.
26. The compound according to claim 25, wherein each strand comprises 20-22 nucleotides.
- 35 27. The compound according to any of the preceding claims, wherein at least one of the strands has a 3' overhang.

28. The compound according to any of the preceding claims, wherein X is selected from the group consisting of O, S and NH.

29. The compound according to claim 28, wherein X is O.

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30. The compound according to any of the preceding claims, wherein said LNA monomer is in the beta-D form.

31. A pharmaceutical composition comprising the compound as defined in any of claims 1-10 30 and a pharmaceutically acceptable diluent, carrier or adjuvant.

32. The pharmaceutical composition according to claim 31, wherein said composition further comprises at least one active agent.

15 33. The pharmaceutical composition according to claim 32, wherein said active agent is a chemotherapeutic agent.

34. The pharmaceutical composition according to claim 33, wherein said chemotherapeutic agent is selected from the group consisting of adrenocorticosteroids, such as prednisone, 20 dexamethasone or decadron; altretamine (hexalen, hexamethylmelamine (HMM)); amifostine (ethyol); aminoglutethimide (cytadren); amsacrine (M-AMSA); anastrozole (arimidex); androgens, such as testosterone; asparaginase (elspar); bacillus calmette-gurin; bicalutamide (casodex); bleomycin (blenoxane); busulfan (myleran); carboplatin (paraplatin); carmustine (BCNU, BiCNU); chlorambucil (leukeran); chlorodeoxyadenosine 25 (2-CDA, cladribine, leustatin); cisplatin (platinol); cytosine arabinoside (cytarabine); dacarbazine (DTIC); dactinomycin (actinomycin-D, cosmegen); daunorubicin (cerubidine); docetaxel (taxotere); doxorubicin (adriamycin); epirubicin; estramustine (emcyt); estrogens, such as diethylstilbestrol (DES); etoposide (VP-16, VePesid, etopophos); fludarabine (fludara); flutamide (eulexin); 5-FUDR (floxuridine); 5-fluorouracil (5-FU); 30 gemcitabine (gemzar); goserelin (zodalex); herceptin (trastuzumab); hydroxyurea (hydrea); idarubicin (idamycin); ifosfamide; IL-2 (proleukin, aldesleukin); interferon alpha (intron A, roferon A); irinotecan (camptosar); leuprolide (lupron); levamisole (ergamisole); lomustine (CCNU); mechlorathamine (mustargen, nitrogen mustard); melphalan (alkeran); mercaptopurine (purinethol, 6-MP); methotrexate (mexate); mitomycin-C (mutamucin); 35 mitoxantrone (novantrone); octreotide (sandostatin); pentostatin (2-deoxycoryformycin, nipent); plicamycin (mithramycin, mithracin); prorocarbazine (matulane); streptozocin; tamoxifen (nolvadex); taxol (paclitaxel); teniposide (vumon, VM-26); thiotepa; topotecan (hycamtin); tretinoin (vesanoid, all-trans retinoic acid); vinblastine (valban); vincristine (oncovin) and vinorelbine (navelbine).

35. The compound according to any of claims 1-30 for use as a medicament.

36. Use of a compound as defined in any of claims 1-30 for the manufacture of a
5 medicament for the treatment of cancer.

37. Use according to claim 36, wherein said cancer is in the form of a solid tumor.

38. Use according to claim 36 or 37, wherein said cancer is a carcinoma.

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39. Use according to claim 38, wherein said carcinoma is selected from the group
consisting of malignant melanoma, basal cell carcinoma, ovarian carcinoma, breast
carcinoma, non-small cell lung cancer, renal cell carcinoma, bladder carcinoma, recurrent
superficial bladder cancer, stomach carcinoma, prostatic carcinoma, pancreatic carcinoma,
15 lung carcinoma, cervical carcinoma, cervical dysplasia, laryngeal papillomatosis, colon
carcinoma, colorectal carcinoma and carcinoid tumors.

40. Use according to claim 39, wherein said carcinoma is selected from the group
consisting of malignant melanoma, non-small cell lung cancer, breast carcinoma, colon
20 carcinoma and renal cell carcinoma.

41. Use according to claim 40, wherein said malignant melanoma is selected from the
group consisting of superficial spreading melanoma, nodular melanoma, lentigo maligna
melanoma, acral melanoma, amelanotic melanoma and desmoplastic melanoma.
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42. Use according to claim 36 or 37, wherein said cancer is a sarcoma.

43. Use according to claim 42, wherein said sarcoma is selected from the group consisting
of osteosarcoma, Ewing's sarcoma, chondrosarcoma, malignant fibrous histiocytoma,
30 fibrosarcoma and Kaposi's sarcoma.

44. Use according to claim 36 or 37, wherein said cancer is a glioma.

45. Use of a compound as defined in any of claims 1-30 for the manufacture of a
35 medicament for the treatment of arteriosclerosis, psoriasis, diabetic retinopathy,
rheumatoid arthritis, asthma, warts or allergic dermatitis.

46. Use of a compound as defined in any of claims 1-30 for the manufacture of a
medicament for the treatment of cancer, wherein said medicament further comprises a

chemotherapeutic agent selected from the group consisting of adrenocorticosteroids, such as prednisone, dexamethasone or decadron; altretamine (hexalen, hexamethylmelamine (HMM)); amifostine (ethyol); aminoglutethimide (cytadren); amsacrine (M-AMSA); anastrozole (arimidex); androgens, such as testosterone; asparaginase (elspar); bacillus calmette-gurin; bicalutamide (casodex); bleomycin (blenoxane); busulfan (myleran); carboplatin (paraplatin); carmustine (BCNU, BiCNU); chlorambucil (leukeran); chlorodeoxyadenosine (2-CDA, cladribine, leustatin); cisplatin (platinol); cytosine arabinoside (cytarabine); dacarbazine (DTIC); dactinomycin (actinomycin-D, cosmegen); daunorubicin (cerubidine); docetaxel (taxotere); doxorubicin (adriomycin); epirubicin; estramustine (emcyt); estrogens, such as diethylstilbestrol (DES); etoposide (VP-16, VePesid, etopophos); fludarabine (fludara); flutamide (eulexin); 5-FUDR (floxuridine); 5-fluorouracil (5-FU); gemcitabine (gemzar); goserelin (zodalex); herceptin (trastuzumab); hydroxyurea (hydrea); idarubicin (idamycin); ifosfamide; IL-2 (proleukin, aldesleukin); interferon alpha (intron A, roferon A); irinotecan (camptosar); leuprolide (lupron); levamisole (ergamisole); lomustine (CCNU); mechlorathamine (mustargen, nitrogen mustard); melphalan (alkeran); mercaptopurine (purinethol, 6-MP); methotrexate (mexate); mitomycin-C (mutamucin); mitoxantrone (novantrone); octreotide (sandostatin); pentostatin (2-deoxycoformycin, nipent); plicamycin (mithramycin, mithracin); prorocarbazine (matulane); streptozocin; tamoxifen (nolvadex); taxol (paclitaxel); teniposide (vumon, VM-26); thiotepa; topotecan (hycamtin); tretinoin (vesanoid, all-trans retinoic acid); vinblastine (valban); vincristine (oncovin) and vinorelbine (navelbine).

47. The use according to claim 46, wherein the chemotherapeutic agent is taxol (paclitaxel).

48. Use of a compound as defined in any of claims 1-30 for the manufacture of a medicament for the treatment of cancer, wherein said treatment further comprises the administration of a further chemotherapeutic agent selected from the group consisting of adrenocorticosteroids, such as prednisone, dexamethasone or decadron; altretamine (hexalen, hexamethylmelamine (HMM)); amifostine (ethyol); aminoglutethimide (cytadren); amsacrine (M-AMSA); anastrozole (arimidex); androgens, such as testosterone; asparaginase (elspar); bacillus calmette-gurin; bicalutamide (casodex); bleomycin (blenoxane); busulfan (myleran); carboplatin (paraplatin); carmustine (BCNU, BiCNU); chlorambucil (leukeran); chlorodeoxyadenosine (2-CDA, cladribine, leustatin); cisplatin (platinol); cytosine arabinoside (cytarabine); dacarbazine (DTIC); dactinomycin (actinomycin-D, cosmegen); daunorubicin (cerubidine); docetaxel (taxotere); doxorubicin (adriomycin); epirubicin; estramustine (emcyt); estrogens, such as diethylstilbestrol (DES); etoposide (VP-16, VePesid, etopophos); fludarabine (fludara); flutamide (eulexin);

5-FUDR (floxuridine); 5-fluorouracil (5-FU); gemcitabine (gemzar); goserelin (zodalex); herceptin (trastuzumab); hydroxyurea (hydrea); idarubicin (idamycin); ifosfamide; IL-2 (proleukin, aldesleukin); interferon alpha (intron A, roferon A); irinotecan (camptosar); leuprolide (lupron); levamisole (ergamisole); lomustine (CCNU); mechlorethamine
 5 (mustargen, nitrogen mustard); melphalan (alkeran); mercaptopurine (purinethol, 6-MP); methotrexate (mexate); mitomycin-C (mutamycin); mitoxantrone (novantrone); octreotide (sandostatin); pentostatin (2-deoxycoformycin, nipent); plicamycin (mithramycin, mithracin); prorocarbazine (matulane); streptozocin; tamoxifen (nolvadex); taxol (paclitaxel); teniposide (vumon, VM-26); thiotepa; topotecan (hycamtin); tretinoin
 10 (vesanoid, all-trans retinoic acid); vinblastine (valban); vincristine (oncovin) and vinorelbine (navelbine).

49. The use according to claim 48, wherein the chemotherapeutic agent is taxol (paclitaxel).

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50. A method for treating cancer, said method comprising administering a compound as defined in any of claims 1-30 or a pharmaceutical composition as defined in any of claims 31-34 to a patient in need thereof.

20 51. The method according to claim 50, wherein said cancer is in the form of a solid tumor.

52. The method according to claim 50 or 51, wherein said cancer is a carcinoma.

25 53. The method according to claim 52, wherein said carcinoma is selected from the group consisting of malignant melanoma, basal cell carcinoma, ovarian carcinoma, breast carcinoma, non-small cell lung cancer, renal cell carcinoma, bladder carcinoma, recurrent superficial bladder cancer, stomach carcinoma, prostatic carcinoma, pancreatic carcinoma, lung carcinoma, cervical carcinoma, cervical dysplasia, laryngeal papillomatosis, colon carcinoma, colorectal carcinoma and carcinoid tumors.

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54. The method according to claim 53, wherein said carcinoma is selected from the group consisting of malignant melanoma, non-small cell lung cancer, breast carcinoma, colon carcinoma and renal cell carcinoma.

35 55. The method according to claim 54, wherein said malignant melanoma is selected from the group consisting of superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, acral melanoma, amelanotic melanoma and desmoplastic melanoma.

56. The method according to claim 50 or 51, wherein said cancer is a sarcoma.

57. The method according to claim 56, wherein said sarcoma is selected from the group consisting of osteosarcoma, Ewing's sarcoma, chondrosarcoma, malignant fibrous histiocytoma, fibrosarcoma and Kaposi's sarcoma.

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58. The method according to claim 50 or 51, wherein said cancer is a glioma.

59. A method for treating cancer, said method comprising administering a compound as defined in any of claims 1-30 or a pharmaceutical composition as defined in any of claims 31-34 to a patient in need thereof and further comprising the administration of a further chemotherapeutic agent selected from the group consisting of adrenocorticosteroids, such as prednisone, dexamethasone or decadron; altretamine (hexalen, hexamethylmelamine (HMM)); amifostine (ethyol); aminoglutethimide (cytadren); amsacrine (M-AMSA); anastrozole (arimidex); androgens, such as testosterone; asparaginase (elspar); bacillus calmette-gurin; bicalutamide (casodex); bleomycin (blenoxane); busulfan (myleran); carboplatin (paraplatin); carmustine (BCNU, BiCNU); chlorambucil (leukeran); chlorodeoxyadenosine (2-CDA, cladribine, leustatin); cisplatin (platinol); cytosine arabinoside (cytarabine); dacarbazine (DTIC); dactinomycin (actinomycin-D, cosmegen); daunorubicin (cerubidine); docetaxel (taxotere); doxorubicin (adriamycin); epirubicin; estramustine (emcyt); estrogens, such as diethylstilbestrol (DES); etoposide (VP-16, VePesid, etopophos); fludarabine (fludara); flutamide (eulexin); 5-FUDR (floxuridine); 5-fluorouracil (5-FU); gemcitabine (gemzar); goserelin (zodalex); herceptin (trastuzumab); hydroxyurea (hydrea); idarubicin (Idamycin); ifosfamide; IL-2 (proleukin, aldesleukin); interferon alpha (intron A, roferon A); irinotecan (camptosar); leuprolide (lupron); levamisole (ergamisole); lomustine (CCNU); mechlorathamine (mustargen, nitrogen mustard); melphalan (alkeran); mercaptopurine (purinethol, 6-MP); methotrexate (mexate); mitomycin-C (mutamucin); mitoxantrone (novantrone); octreotide (sandostatin); pentostatin (2-deoxycoformycin, nipent); plicamycin (mithramycin, mithracin); prorocarbazine (matulane); streptozocin; tamoxifen (nolvadex); taxol (paclitaxel); teniposide (vumon, VM-26); thiotepa; topotecan (hycamtin); tretinoin (vesanoid, all-trans retinoic acid); vinblastine (valban); vincristine (oncovin) and vinorelbine (navelbine).

60. The method according to claim 59, wherein the chemotherapeutic agent is taxol (paclitaxel).

61. Use of a compound as defined in any of claims 1-30 for the manufacture of a medicament for the treatment of Severe Acute Respiratory Syndrome (SARS).

62. A method for treating Severe Acute Respiratory Syndrome (SARS), said method comprising administering a compound as defined in any of claims 1-30 or a pharmaceutical composition as defined in any of claims 31-34 to a patient in need thereof.

5 63. A method for producing a compound comprising a strand of 12-35 nucleotide monomers, wherein said compound comprises at least one locked nucleic acid (LNA) monomer, and wherein the individual monomers are coupled using 1*H*-tetrazole or 5-ethylthio-1*H*-tetrazole.

10 64. The method according to claim 63, wherein a coupling time in the range of 200-1200 seconds is used.

65. The method according to claim 64, wherein said coupling time is in the range of 400-1200 seconds.

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66. The method according to claim 65, wherein said coupling time is in the range of 600-900 seconds.